Ethical, Social, and Legal Issues Surrounding Studies of Susceptible Populations and Individuals

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Calls for professional accountability have resulted in the development of ethics guidelines by numerous specialty and subspecialty groups of scientists. Indeed, guidelines among some health professions now address vulnerable and dependent groups; but these are silent on issues related to biomarkers. In parallel, attention has been drawn to human rights concerns associated with attempts to detect hypersusceptible workers, especially in democratic countries. Despite this, concern for vulnerable populations grows as advances in biomarker technology make the identification of genetic predisposition and susceptibility markers of both exposure and outcome more attainable. In this article, the principles derived from the ethical theory of utilitarianism provide the basis for principle-based ethical analysis. In addition, the four principles of biomedical ethics—respect for autonomy, beneficence, nonmaleficence, and social justice—are considered for biomarker studies. The need for a context in which ethical analysis is conducted and from which prevailing social values are shown to drive decisions of an ethical nature is emphasized; these include statutory regulation and law. Because biomarker studies can result in more harm than good, special precautions to inform research participants prior to any involvement in the use of biomarkers are needed. In addition, safeguards to maintain the privacy of data derived from biomarker studies must be developed and implemented prior to the application of these new technologies. Guidelines must be expanded to incorporate ethical, social, and legal considerations surrounding the introduction of new technologies for studying susceptible populations and individuals who may be vulnerable to environmental exposures. — *Environ Health Perspect* 105(Suppl 4):837–841 (1997)

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Introduction to Professional Conduct

The need, among others, to be publicly accountable has led many professions to develop guidelines, declarations, or codes of ethics and, in some instances, standards of practice. These statements on appropriate professional conduct document the normative practices against which the profession can be held accountable for its actions, both collectively and by its individual practitioners (*1*).

The phenomenon of developing codes/guidelines is relatively recent, having become common practice within only the past decade. Hence, many of the codes are very recent, e.g., those promulgated by the International Commission on Occupational Health (ICOH) (*2*) and the Council for International Organizations of Medical Sciences (CIOMS) (*3,4*). It is therefore useful to examine them to see what guidance has been incorporated on issues dealing with susceptible groups of people and/or individuals. Of particular note is the attention given in these recent documents to vulnerable populations.

Advances in professional (or, applied) ethics are made by thoughtful and innovative thinkers (or, visionaries) in any activity area within the broad array of professional endeavor. However, it is only once the deliberations of these so-called visionaries are ultimately integrated into the profession's codes/guidelines, that they will be deemed "common practice," or normative. Hence, this article also examines the more recent published and presented works by leading contributors to the philosophy of biomarkers for the screening of populations (*5–66*). The latter exercise is intended to identify future ethical, social, and legal directions in the area of studies of susceptible populations and individuals. Matters that focus directly on the science and/or technology of biomarkers do not fall within the scope of this article.

Extant Guidelines

The four principles upon which much health-related ethical analysis is conducted are respect for autonomy (respect for persons, embracing the need for prior, voluntary, fully informed consent), beneficence (doing good), nonmaleficence (doing no harm), and distributive justice (social justice or equity vis à vis the equal allocation of risks and benefits).

While recent international guidelines are silent on the issue of biomarker studies per se, the CIOMS (1991) guidelines do state, consistent with the principle of nonmaleficence, that harm to the individual should be minimized (*3*). Specifically (and of relevance to genetic testing), "Ethical review must always assess the risk of subjects or groups suffering stigmatization, prejudice, loss of prestige or self-esteem, or economic loss as a result of taking part in a study..." (principle 19). With regard to groups (principle 21), "Epidemiological studies may inadvertently expose groups as well as individuals to harm, such as economic loss, stigmatization, blame, or withdrawal of services. Investigators who find sensitive information that may put a group at risk of adverse criticism or treatment should be discreet in communicating and explaining their findings...."

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In preparing this paper, I have drawn heavily on material published by the International Commission on Occupational Health, Council for International Organizations of Medical Sciences, and, in particular, papers of Paolo Vineis, among others, contained in the bibliography.

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Abbreviations used: CIOMS, Council for International Organizations of Medical Sciences; ICOH, International Commission on Occupational Health

Concerning "vulnerable and dependent groups," the CIOMS (1991) guidelines state:

> Ethical review committees should be particularly vigilant in the case of proposals involving populations primarily of children, pregnant and nursing women, persons with mental illness or handicap, members of communities unfamiliar with medical concepts, and persons with restricted freedom to make truly independent choices, such as prisoners and medical students. Similar vigilance is called for in the case of proposals for invasive research with no direct benefit to its subjects (principle 43) (*4*).

It is only the latter portion of this principle that could be seen to be of particular relevance to biomarker research and its applications. CIOMS (1993) addresses this issue under its guideline no. 10, "Selection of research subjects: equitable distribution of burdens and benefits." It states, " ... Special justification is required for inviting vulnerable individuals and, if they are selected, the means of protecting their rights and welfare must be particularly strictly applied."

On the subject of "biological monitoring and investigations," (principle 12) the most relevant guidelines for professionals engaged in occupational health and safety (ICOH, 1996) states:

> Biological tests and other investigations must be chosen from the point of view of their validity for protection of the health of the worker concerned, with due regard to their sensitivity, their specificity and their predictive value. Occupational (and environmental) health professionals must not use screening tests or investigations which are not reliable or which do not have a sufficient predictive value in relation to the requirements of the work assignment. Where a choice is possible and appropriate, preference must always be given to noninvasive methods and to examinations which do not involve any danger to the health of the worker concerned. An invasive investigation or an examination which involves a risk to the health of the worker concerned may only be advised after an evaluation of the benefits and the risks involved and cannot be justified in relation to insurance claims. Such an investigation is subject to the worker's informed consent and must be performed according to the highest professional standards.

[Note: Because the ICOH document confines itself to occupationally exposed groups, all quoted statements from this document will be expanded to incorporate environmental health where appropriate, in parentheses within any quotation.]

Guidelines are not an end in themselves; they are expected to be reviewed and revised from time to time to reflect changing values and to rise to the challenge presented from advances in technology that so often precipitate the need for concern about ethical conduct. With biomarker technology gaining prominence, a lag of some years can be anticipated before the ethics guidelines/codes of conduct are seen to address related issues.

Social and Legal Perspectives

The context for considering ethical issues is important for the analysis of an ethical dilemma. Context can shed light on which ethical principles ought to take precedence over others. Hence, the context of occupational and environmental health will be addressed first.

The aim of occupational and environmental health practice is to protect health and to promote the establishment and maintenance of a safe and healthy environment. In addition, in the occupational health context in particular, the aim is to promote the adaptation of work to the capabilities of workers, taking into account their state of health. Attention in guidelines thus should be given to vulnerable groups and to underserved working populations (*43*). Occupational health is essentially preventive and should help the workers, individually and collectively, to safeguard their health in their employment. It should thereby help the enterprise to ensure healthy and safe working conditions and environment, which are criteria of efficient management and are to be found in well-run enterprises.

The field of occupational health is comprehensive and covers the prevention of all impairments arising out of employment, work injuries, and work-related diseases as well as all aspects relating to the interactions between work and health. Occupational health professionals should be involved, whenever possible, in the design of health and safety equipment, methods, and procedures and they should encourage workers' participation in this field. Occupational health professionals have a role to play in the promotion of workers' health and should assist workers in obtaining and maintaining employment notwithstanding their health deficiencies or their handicap. The word "workers" is used here in a broad sense and covers all employees, including management and the self-employed.

The approach in both occupational and environmental health is multidisciplinary and intersectoral. There is a wide range of obligations and complex relationships among those concerned (*2*). It is therefore important to define the role of professionals and their relationships with other professionals, with other health professionals and with social partners in the purview of economic, social, and health policies development. This calls for a clear view about the ethics of occupational and/or environmental health professionals and standards in their professional conduct.

In occupational settings in general, duties and obligations are defined by statutory regulations. Each employer has the responsibility for the health and safety of the workers in his or her employment. In particular, in the United States it is the obligation of the employer to provide a safe and healthful workplace (*67*). More recent interpretation of this legislation points to environmental control as opposed to worker exclusion for meeting this obligation.

Each profession has its responsibilities that are related to the nature of its duties. When specialists of several professions are working together within a multidisciplinary approach, it is important that they base their action on some common principles of ethics and that they have an understanding of each others' obligations, responsibilities and professional standards. Special care should be taken with respect to ethical aspects, in particular when there are conflicting rights such as the right to the protection of employment and the right to the protection of health, the right to information and the right to confidentiality, as well as individual rights and collective rights (*2*).

Some of the conditions of execution of the functions of occupational health professionals and the conditions of operation of occupational health services are often defined in statutory regulations. One of the basic requirements for a sound occupational health practice is full professional independence, i.e., that occupational health professionals must enjoy independence in the exercise of their functions that should enable them to make judgments and give advice for the protection of the workers' health and for their safety within the undertaking in accordance with their knowledge and conscience (*2*). The analogous arguments could be made in support of the

independence of the environmental health practitioner in protecting the interests of public health.

There are basic requirements for acceptable occupational health practice. These conditions of operation are sometimes specified by national regulations and include, in particular, free access to the work place, the possibility of taking samples and assessing the working environment, making job analyses and participating in inquiries after an accident, and the possibility to consult the competent authority on the implementation of occupational safety and health standards in the undertaking. Occupational health professionals should be allocated a budget that will enable them to carry out their functions according to good practice and to the highest professional standards. This should include adequate staffing, training, and retraining; support, and access to relevant information and to an appropriate level of senior management (*2*). These arguments can be extended to environmental health professionals.

Ethical Considerations

Ethical analysis often points to tensions between two or more principles. For example, the need for individual privacy can conflict with the need to protect the public interest; and, the need to do good has to be balanced against the potential also to cause harm. Because of this, a review of the strengths and weaknesses of the advances that biomarker technology brings must be considered.

Epidemiology has relied on hard end points such as death in most cohort studies. However, workers might prefer to see something different from body counts when the potential health effects of occupational exposures are studied (*31,57*). Likewise, the public might prefer to see something different from body counts when the potential health effects from environmental exposures are studied. Therefore, more direct indicators of both exposure and early response (or outcome) would have some advantages. Biological markers provide just such a tool.

The use of biological markers, such as lead levels in blood or liver function tests, is not new in occupational or environmental epidemiology. However, the use of molecular techniques in epidemiological studies has made possible the use of biomarkers to assess target organ exposure for determining susceptibility and for establishing early disease.

Potential uses of biomarkers in the context of occupational and environmental epidemiology include the following (*31,57*):

- exposure assessment in cases in which traditional epidemiologic tools are insufficient (particularly for low doses and low risks)
- multiple exposures or mixtures, in which the aim is to disentangle the causative role of single chemical agents or substances
- estimation of the total burden of exposure to chemicals that have the same mechanistic target
- investigation of pathogenetic mechanisms
- study of individual susceptibility (e.g., metabolic polymorphisms, DNA repair)
- an increase in statistical power owing to more accurate classification of exposure and/or disease.

In reference to the latter point, biomarkers can be highly specific indicators of a cause of a disease that otherwise has multiple causes. For example, determination of the relationship among specific patterns of chromosomal abnormalities in chemical-induced leukemia can improve the likelihood of determining a cause-and effect-relationship in a cluster of leukemias or, as another example, study of the codons involved in *p53* mutations could lead to distinguishing between those lung cancers from radon and those from cigarette smoking, a point of much value in determining radon risk.

Great enthusiasm has arisen in the scientific community about these uses but, as noted above, methodological complexity should serve to caution against excessive optimism. Biomarkers of chemical exposures (such as DNA adducts) have several shortcomings (*31,35,57*).

a) They usually reflect recent exposures and, therefore, are of limited use in case–control studies, whereas they require repeated samplings over prolonged periods for use in cohort investigations. *b*) While they can be highly specific and thus improve exposure classification, findings often remain difficult to interpret. *c*) When complex chemical exposures, e.g., air pollution or environmental tobacco smoke are investigated, it is possible that the biomarker would reflect one particular component of the mixture, whereas the biological effect, in fact, could have arisen from another component of the mixture. *d*) In many situations, it is not clear whether a biomarker reflects a relevant exposure, a correlate of the relevant exposure, individual susceptibility, or an early disease stage, thus limiting causal inference. *e*) The determination of most biomarkers requires an expensive test or an invasive procedure or both, thus creating constraints for adequate study size and statistical power. *f*) A biomarker of exposure is no more than a proxy for the real objective of an epidemiological investigation which, as a rule, focuses on an avoidable environmental exposure (*31,56,57*).

Even more important than the methodological shortcomings is the consideration that molecular techniques might cause us to redirect our focus from identifying risks in the exogenous environment to identifying high-risk individuals and then making personalized risk assessments by measuring phenotype, adduct load, and acquired mutations. This would direct our focus to a form of clinical evaluation rather than one of public health epidemiology. Focusing on individuals could distract us from the important public health goal of creating a less hazardous environment. Clearly, there are both potential benefits and potential harms from the use of biomarker technology.

At least two early critiques of the view that supported the advancement of technologies whose goal it was to detect hypersusceptible workers have pointed to the sociopolitical context of such technologies (*10,16*). In fact, Green (*16*) examined the earlier concept of the hypersusceptible worker, arguing that the "concept enabled industrial toxicologists to organize knowledge about workers' reactions to toxicity so as to sustain a professional and methodological ideology which reflects the relationship between industrial toxicology and capitalist industry." Atherley (*10*) presents an example (i.e., lead) of the erosion of human rights by certain legislated activities in occupational medicine, concluding that issues relating to medical monitoring comprise political and ethical issues, not merely technical ones, that should be debated publicly. Both Green and Atherley, whether invoking examples from audiometry and radiographs (X-rays) of the back to glucose 6-phosphate dehydrogenase and serum-α-1-antitrypsin deficiency, conclude that none of these markers satisfy even those criteria specified by the proponents of such tests (*10,16*); this view also has more recent support (*56,57*).

Ethical Directions

Two further important issues emerge regarding the use of biomarkers (*31*). First,

the use of biomarkers in both occupational and environmental epidemiology must be accompanied by a clear policy as far as informed consent is concerned. In the occupational setting, the worker may have several reasons to refuse cooperation. One very practical reason is that the identification of, say, an alteration in an early response marker (such as sister chromatid exchange) is not recognized by insurance companies as an occupational disease, but private insurers might shun the worker because he/she may be more prone to disease. A second reason concerns genetic screening: since the distributions of genotypes and phenotypes vary according to ethnic group, occupational opportunities for minorities might be hampered by genetic screening. Third, doubts can be raised about the predictability of genetic tests: since the predictive value depends on the prevalence of the condition that the test aims to identify, if the latter is rare, the predictive value will be low and the practical use of the screening test will be questionable, with a high rate of false positives (*12*). To date, none of the genetic screening tests have been judged applicable in the field (*6,10,11,16,35,56*).

The second issue that emerges concerning use of biomarkers is that ethical principles must be applied prior to the use of biomarkers. Recently, these principles were considered for biomarkers used for identifying individual susceptibility to disease. An interdisciplinary Working Group of the Technical Office of the European Trade Unions with the support of the Commission of the European Communities has reinforced the view that tests can be conducted only with the objective of preventing disease in a workforce (*68*). Among other considerations, the use of tests must never *a*) serve as a means for selection of the fittest; *b*) be used to avoid implementing effective preventive measures, notably the need to eliminate or reduce hazardous conditions in the workplace or in the environment; *c*) create, confirm, or reinforce social inequality; *d*) create a gap between the ethical principles followed in the workplace or in the environment and the ethical principles that must be upheld in a democratic society; or *e*) oblige a person seeking employment to disclose personal details other than those strictly necessary for obtaining the job (*57*).

Finally, evidence is accumulating that the metabolic activation or inactivation of hazardous substances (and of carcinogens in particular) varies considerably in human populations and is partly genetically determined. Furthermore, interindividual variability in susceptibility to carcinogens may be particularly important at low levels of occupational and environmental exposure (*59*). The implications of these findings for regulatory decisions that focus the risk assessment process on the most susceptible are obvious (*61*).

Where professional groups are slow or reluctant to exercise due restraint in the application of new technologies (such as biomarkers), governments are likely to intervene with legislation in the public interest. It therefore behooves thoughtful professionals to consider the application of biomarkers in their professional interests and to develop guidelines for their use.

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